Remarks

Claims 127-132 are pending in this application. Claim 127 is amended in this paper to remove the recitation of "prevention" of an affective disorder and the recitation "in need of treatment or prevention." No new matter has been introduced.

A. The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

On pages 2-7, claims 127-132 are rejected as allegedly not enabled. In particular, it is alleged that the specification, "while being enabling for TREATING an affective disorder," is not enabling for prevention of such a disorder. (Office Action, page 3). Although Applicants respectfully disagree, especially since the specification provides sufficient guidance as to how those skilled in the art may make and practice the claimed method of prevention, the recitation with regard to prevention is deleted from claim 127 solely to expedite the prosecution of this application. In view of this amendment, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

B. The Rejection Under 35 U.S.C. § 103(a) Over Morgan and Spier Should Be Withdrawn

On pages 7-9 of the Office Action and in the Advisory Action, claims 127-132 are rejected as allegedly obvious over U.S. Patent No. 6,274,579 to Morgan *et al.* ("Morgan"), in view of Spier *et al.*, *Depression and Anxiety*, 7: 73-75 (1998) ("Spier")[1]. In particular, based on the allegation that "Spier teaches a combination drug of bupropion and SRIs in the treatment of depression," and "Morgan teaches that bupropion's anti-depressant activity is resulted from the active metabolite," it is alleged that "one would have been motivated ... to add SSRI or 5HT compound as secondary active compound." (Office Action, pages 8-9). Further, the Examiner, citing WO 99/17083 to Cary Medical Corporation ("Cary"), U.S. Patent No. 6,677,378 to Howard, Jr. *et al.* ("Howard"), the abstract of Zarate, *Bipolar Disorder*, 5(3): 217-225 (2003) ("Zarate") and Post *et al.*, *Depression and Anxiety*, 5(4): 175-189 (1997) ("Post"), alleges that a motivation to combine/modify existed. (*Id.*, page 9). Applicants respectfully disagree with each of these allegations.

[1] The Office Action cites the abstract of Spier. A copy of the full article is provided herein for the Examiner's consideration.

As the Examiner indicates, Spier discloses that combination of bupropion and SRI or venlafaxine may be effective in certain patients who are inadequately responsive to monotherapies. (Spier, Abstract). However, Spier is silent as to the use of a bupropion metabolite. Despite this, the Examiner appears to consider that those skilled in the art would have been motivated to replace the bupropion, as used in the combination disclosed in Spier, with a bupropion metabolite in view of Morgan's disclosure that "the anti-depressant activity of [racemic bupropion] is likely to result from the effects of" (S,S)-hydroxybupropion." (Morgan, col. 8, lines 15-17). Applicants respectfully disagree.

Applicants respectfully point out that although Morgan reports that the anti-depressant activity of racemic bupropion is likely to result from (S,S)-hydroxybupropion, it does not provide any motivation to those skilled in the art to replace bupropion with (S,S)-hydroxybupropion in any and all methods where bupropion is used. This is because Morgan fails to disclose that (S,S)-bupropion would be more advantageous than racemic bupropion in any and all instances. For example, Morgan discloses that, while (S,S)-hydroxybupropion "was approximately twice as potent as [racemic bupropion] as an NA inhibitor," it was "approximately 10-fold less potent as an inhibitor of dopamine uptake." (Morgan, col. 7, lines 25-29). Therefore, at most, Morgan merely shows that (S,S)-hydroxybupropion has different, but not necessarily more desirable, pharmacological properties than racemic bupropion.

Further in this regard, Morgan also discloses that "the mechanism of action of bupropion, as with other antidepressants, is unknown." (Morgan, col. 1, lines 24-25). Therefore, by disclosing that bupropion's mechanism of action was not well-understood, and that (S,S)-hydroxybupropion has properties merely different than those of bupropion, Morgan certainly does not teach or suggest that (S,S)-hydroxybupropion can replace bupropion in all of the uses contemplated for bupropion.

In addition, even assuming, *arguendo*, that Morgan somehow suggested that (S,S)-hydroxybupropion can replace bupropion in all of the uses, those skilled in the art would still not have been motivated to use (S,S)-hydroxybupropion for the method disclosed in Spier. This is because Morgan shows that bupropion and (S,S)-hydroxybupropion possess substantially similar anti-depressant activity as

determined by TBZ test.[2] (*See* Morgan, FIG. 1). Therefore, while the disclosure of Morgan may have provided a basis to conclude that the anti-depressant activity of racemic bupropion is "likely to result from the effects of" (S,S)-hydroxybupropion, such a disclosure would not have provided any motivation to those skilled in the art to use (S,S)-hydroxybupropion instead of bupropion in the method disclosed in Spier, especially when Morgan itself teaches that the two compounds' anti-depressant activities are substantially similar.

Finally, the Examiner appears to indicate that references such as Cary, Howard, Zarate[3] and Post would have provided motivation to combine and modify Morgan and Spier to arrive at the claimed invention. The Examiner alleges that these references show that "combination drug treatment could enhance drug efficacy and improve industrial applicability as well." (Office Action, page 9). Even if taken true, such a disclosure does not provide any specific motivation or reasonable expectation of success to those skilled in the art with regard to any specific combination therapies, much less those claimed herein.

For example, Cary, by disclosing bupropion (but not a bupropion metabolite) as one of many "anti-depressants" that can allegedly be used for the treatment of nicotine addiction, does not provide any specific motivation with regard to the claimed method. Howard, by disclosing a genus of compounds, which is completely different from bupropion or a bupropion metabolite, also does not provide any motivation.

More importantly, Post clearly shows the state of the art at the time of this invention, thereby establishing that no specific motivation or suggestion existed with regard to any specific combination therapy, much less the method recited by the pending claims. In this regard, Post discloses, referring to combination therapies for bipolar depression, that there are "a panoply of treatment options now exist," and states that these potential therapies' "relative efficacy in different illness subtypes and stages remains to be better delineated, as do their optimal sequencing and use in combination in individual patients." (Post, page 184, under "Summary and

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[2] In fact, FIG. 1 appears to show that anti-depressant activity of racemic bupropion, as determined by TBZ test, is slightly higher (*i.e.*, lower TBZ score) than (S,S)-hydroxybupropion.

[3] Applicants respectfully point out that Zarate is not prior art.

Conclusion") (emphasis added). In addition, Post states that when using combination therapies, "one has to be particularly careful about drug interactions and their potential for toxicity as well as therapeutic effects." (*Id.*). Post also teaches that "one should be aware of potential pharmacokinetic interactions" when using a combination therapy. (*Id.*). As can be seen from these statements, Post clearly teaches that no generalization can be made regarding any specific combination therapies for affective disorders. Consequently, quite contrary to what the Examiner alleges, Post actually attests to the fact that the Morgan and Spier cannot establish a *prima facie* obviousness of the claimed invention.

For at least the foregoing reasons, Applicants respectfully submit that no prima facie obviousness is established by Morgan and Spier, and thus request that the rejection of the claims be withdrawn.

C. The Rejection Under 35 U.S.C. § 103 Over Howard or Cary in View of Morgan Should Be Withdrawn

On pages 9-11 of the Office Action, claims 127-132 are rejected as allegedly obvious over Howard or Cary, in view of Morgan. Applicants respectfully traverse this rejection. Specifically, Applicants respectfully submit that no *prima facie* case of obviousness is established by the references cited by the Examiner.

It appears that the Examiner's allegation of obviousness is premised on the following assertions: 1) Howard or Cary discloses the claimed methods except that the claims differ from Howard or Cary "in that they require bupropion's metabolite rather than bupropion itself"; and 2) Morgan would have provided motivation to replace bupropion with a bupropion metabolite, based on Morgan's disclosure that bupropion's anti-depressant activity is likely to result from (S,S)-hydroxybupropion. (Office Action, page 10). Applicants respectfully disagree with each of these assertions.

First, the Examiner alleges that Howard teaches the use of SSRIs "in the treatment of affective disorders such as major depressive disorder." (Office Action, page 10). It is further alleged that since Howard "teaches an advantage obtained from a combination drug treatment of SSRI and bupropion," Howard discloses the use of the combination of bupropion and an SSRI for the treatment of an affective disorder.

However, Applicants respectfully submit that the alleged "advantage," as disclosed in Howard, could not have directed those skilled in the art to combine the genus of SSRI disclosed in Howard with bupropion. This is because although Howard states, in the background section, that evidence "has indicated that the sexual dysfunction associated with SSRI therapy can be reduced through the use of dopamine reuptake inhibitors such as bupropion," Howard is completely silent as to whether the genus of SSRIs it discloses can indeed be used in combination with any other active agents, much less bupropion. (Howard, col. 1, lines 27-32). Therefore, Howard does not disclose, suggest, or provide any motivation as to the use of any second active agents, much less bupropion, in combination with the SSRIs it discloses.[4]

Furthermore, even assuming, *arguendo*, that Howard somehow suggested the use of bupropion in combination with the genus of SSRIs it discloses, Howard and Morgan, when considered together, could not have motivated those skilled in the art to replace bupropion with a bupropion metabolite. This is because the portion of Howard relied on by the Examiner specifically discloses that "sexual dysfunction associated with SSRI therapy can be reduced through the use of dopamine reuptake inhibitors, such as bupropion." (*Id.*) (emphasis added). This clearly implies that the "advantage" in combining bupropion with SSRI therapy results from bupropion's activity as a dopamine reuptake inhibitor. Yet, Morgan discloses that (S,S)-hydroxybupropion is "approximately 10 fold less potent as an inhibitor of dopamine uptake" than racemic bupropion. (Morgan, col. 7, lines 26-28). Based on the disclosures of Howard and Morgan, those skilled in the art would not have been motivated to use a bupropion metabolite, which has a much lower dopamine reuptake inhibitor activity, in the place of bupropion, which has a much higher dopamine reuptake inhibitor activity. Thus, Applicants respectfully submit that no *prima facie* case of obviousness is established by Howard and Morgan. Therefore, Applicants respectfully request that the rejection of the claims, to the extent it is based on Howard and Morgan, be withdrawn.

Second, Applicants also submit that the combination of Cary and Morgan also does not render the claimed methods obvious. In this regard, the

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[4] This is more so when considered in view of Post's disclosure that no generalization can be made as to any specific combination.

Examiner alleges that Cary "teaches a nicotine or other addiction treatment ... by applying a combination drug regimen where bupropion and nicotine receptor antagonists ... are effectively used as active agent[s]." (Office Action, page 10). Applicants respectfully disagree.

Cary purportedly discloses "a pharmaceutical composition for treating tobacco addition and nicotine addiction" comprising a "combination of a nicotine receptor antagonist and either an antidepressant or an anti-anxiety drug."[5] (Cary, page 6, lines 2-6). Bupropion is disclosed as one of several possible anti-depressants. Therefore, those skilled in the art would not have been specifically motivated to arrive at the combination of bupropion and another active agent in the first place.

Furthermore, and perhaps more importantly, those skilled in the art, even if they somehow arrived at such a combination (*i.e.*, bupropion and another active agent), would not have been motivated to replace bupropion with a bupropion metabolite, for the reasons discussed above. (In particular, *see* discussion re Post, *supra*). Therefore, Applicants respectfully submit that the combination of Cary and Morgan does not render the claimed methods obvious, and thus request that the rejection of the claims, to the extent it is based on Cary and Morgan, be withdrawn.

D. The Double Patenting Rejection Should Be Withdrawn

On pages 11-12 of the Office Action, the claims are provisionally rejected under judicially created non-statutory double patenting as allegedly unpatentable over the claims in the co-pending Application No. 09/987,930 ("the '930 application") in view of Spier, Howard or Cary. Without addressing the substance of this rejection, Applicants respectfully request that this rejection be held in abeyance until the allowable subject matter in its final form is identified in this and the '930 application. Applicants will file a terminal disclaimer, if necessary, at an appropriate time.

[5] Although the treatment of nicotine or tobacco addiction is not recited by the pending claims, Cary discloses that the compositions it discloses for the treatment of such addictions "may be similar to" those for alcohol or cocaine addiction, which are recited by the pending claims.

Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and request that rejections of the claims be withdrawn.

No fee is believed due for this submission. Should any additional fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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